• Why a metrics program?
• Goals of a metrics program
• Types of metrics
• Further analytics on metrics
• Metrics program design
• Metrics program implementation
• Final thoughts
“Measurement is the first step that leads to control and eventually to improvement. If you can’t measure something, you can’t understand it. If you can’t understand it, you can’t control it. If you can’t control it, you can’t improve it.”
— H. James Harrington
A formal Performance Metrics Program brings value because it.....

1. Provides a clear link and focus to strategy and strategy realization
2. Creates alignment, transparency, and accountability at all levels in the organization
3. Enables a focus on continuous improvement efforts where they have the most impact
4. Enables fact based decisions – not “gut feel” - You can’t improve what you don’t measure
5. Creates a common language to assess and improve performance

Industry Status: Demonstrating Value with Performance Metrics and Continuous Improvement

DIA EDM San Diego: Fall 2013
Steve Gens, Managing Partner, Gens and Associates, Inc.

Produced by TMF Reference Model
GOALS OF A METRICS PROGRAM
Goals of a Metrics Program

1. Provide insight into the ongoing status and quality of a trial
2. Provide insight into overall trends to support process improvements
3. Allow a CRO to report statistics to their sponsor
4. Allow the comparison of a sponsor's CROs against their Service Level Agreements
5. Support planning for future studies (headcount, timeframes...)
6. Allow a sponsor or CRO to monitor performance of specific departments or groups
7. Allow a sponsor or CRO to monitor performance against the industry as a whole
8. Allow the comparison of a sponsor's CROs against each other

-- according to a recent informal survey
TYPES OF METRICS
# Types of TMF Metrics

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>Indication of whether TMFs have defined ownership and planning measures in place</td>
</tr>
<tr>
<td>Completeness</td>
<td>Extent to which a TMF/eTMF contains all documents that are expected at the current point in the study (usually based on last milestone date), or, for completed trials, at the end of the trial.</td>
</tr>
<tr>
<td>Quality</td>
<td>Measure of whether document content, metadata, and indexing are complete and accurate</td>
</tr>
<tr>
<td>Timeliness</td>
<td>Indication of whether documents are available when expected or needed, and of how long documents take to finalize</td>
</tr>
<tr>
<td>Use</td>
<td>Measure of how frequently an electronic TMF system is accessed</td>
</tr>
<tr>
<td>Volume</td>
<td>Measures of the types, numbers and sizes of documents in a TMF/eTMF</td>
</tr>
</tbody>
</table>
• **Completeness**: so that the authorities can reconstruct the trial and ensure GCP compliance

• **Timeliness**: so that accurate decisions can be made based on close to real-time information

• **Quality**: so all parties can have confidence in the documented processes and data
“Procedures should be in place … to assure that the TMF is complete and accurate.” - EMA Reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials

But… how do you measure completeness?

– To know what’s missing, you must know what is expected
– Different for every trial
– Changes of the course of the trial
– For paper TMFs, tracked in a highly manual way
TMF Completeness – what do you measure?

- TMF Completeness assesses if all anticipated documents are collected for trial.
  - Comparison of anticipated content index to filed content
  - Manual process for paper trials
- eTMF facilitates completeness metrics
  - Visual signals for audit / inspection readiness
  - Take action before milestones are missed
  - Real time course corrections and identification of trends
- TMFs completeness can also be measured across programs
  - are all TMFs accounted for and well controlled throughout their lifecycle?
“The TMF should to be up to date, with documents placed in the TMF in a timely manner with the aim to maintain the TMF “inspection ready”.” – EMA Reflection paper

- How do you know when documents are due?
  - Most documents can be tied to a milestone
  - Best case: monitor documents against due dates
  - Next best: monitor to ensure documents tied to milestone are received by milestone due dates
  - Better than nothing: all received before TMF can be closed out and archived
Timeliness – What Do You Measure?

• **Compliance with protocol and study timeline**
  – Is content created, finalized and filed in alignment with timeline and study processes?

• **Timely availability of documents**
  – Is a document collected and filed/uploaded in a timely manner so that it can be generally available by its due date?

• **Effectiveness of processes**
  – Is a document quality checked and finalized in a timely manner after receipt?
  – Do bottlenecks inhibit timely process flow?
“Failure to fully document and perform effective QC checks on documents uploaded into eTMF – the result being that the inspectors had no confidence that the eTMF was accurate. Discrepancies were seen, as were missing pages, incorrect documents, poor quality scans.”

- reported in EMA Reflection paper

“… recommendation that there are regular reviews is to ensure that the documents remain accessible, readable, are filed/named appropriately, so that if there are any issues with the process, individuals utilising the system or the functioning of the system itself, they may be detected and managed. We have seen issues on inspection where scanned documents have not been readable, or not been complete.”

- Clarification provided in email by MHRA
• Accuracy and completeness of documents
  – Missing signatures, inaccurate dates, incorrect annotations

• Accuracy of file location / eTMF indexing
  – Document filed in the correct location
  – Accuracy of metadata for eTMF – assigned to correct trial, site, doc type, etc.

• For scanned content, accuracy and completeness of visual image
  – Defects such as missing/extra pages, skewing, etc. must be detected
The Metrics Working Group has defined a total of 21 metrics for consideration.
• Each metric is defined with details to aid in understanding its business value, how it should be computed, etc.

• Standard metrics structures defined by the Metrics Champion Consortium were taken into consideration and augmented with TMF specific information
Defining Metrics (1 of 2)

- Metric Title
- Metric Type (completeness, quality, etc.)
- Definition
- Metric Indicator
  - **Leading**: shows opportunity for change within a current trial based on that reported metric. They are predictive and can provide forward-looking glimpses into the progression of a trial.
  - **Lagging**: shows opportunity for change in a future trial based on results of previous trials. They are statements of what has already occurred, and are best looked at to evaluate performance for future trials. They are results instead of a prediction.
• Part of Study (Start Up, Conduct, Close-Out)
• Business Driver / Benefit Statement
• Formula / Example
• Reporting Frequency: recommendation on how often metric should be measured and reported
• Notes on eTMF vs. Paper
• General Notes
## Metrics Example: Completeness by Due Date

<table>
<thead>
<tr>
<th>Metric #</th>
<th>Metric Type</th>
<th>Metric Title</th>
<th>Category</th>
<th>Metric Indicator</th>
<th>Part of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Completeness</td>
<td>TMF % Complete by Due Date</td>
<td>N/A</td>
<td>Lagging</td>
<td>Conduct</td>
</tr>
</tbody>
</table>

**Definition**

Percent of documents whose due date has passed that have undergone all necessary review, approval or QC processes and are considered final.

**Formula / Example**

Count of documents due by today’s date that have been finalized / count of documents that were expected by today’s date and

**Reporting Details**

Study / Country / Site / Sponsor / CRO / Function (Zone) / Milestone / CRA / Process / Document Type

**Unit of Measure**

Percentage

**Business Driver / Benefit Statement**

Ensure that the TMF is complete for purpose of decision-making and audit readiness at all times.

**Additional Analysis on a “for cause” basis**

**Reporting Frequency**

Monthly or in advance of milestones

**Threshold Target**

Defined by organization

**Companion Metrics**

Quality metrics, as driving higher completeness could compromise quality.

**Notes (eTMF vs. Paper)**

For paper TMFs, manually tracked in spreadsheet. For eTMFs, system should be able to determine as long as the system knows what is expected and when.

**Notes (General)**

Do not count documents received by today’s date but not yet due by today’s date.

Produced by TMF Reference Model
<table>
<thead>
<tr>
<th>Metric #</th>
<th>Metric Type</th>
<th>Metric Title</th>
<th>Category</th>
<th>Metric Indicator</th>
<th>Part of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Quality</td>
<td>Content Problems</td>
<td>N/A</td>
<td>Lagging</td>
<td>Conduct, Retrospective</td>
</tr>
</tbody>
</table>

**Definition**

Percent of documents for which quality defects related to content (e.g., missing signatures, incorrect annotations, etc.) were identified during QC processes.

**Formula / Example**

Count of documents returned one or more times for content rework / total documents

**Reporting Details**

Study / Country / Site / Sponsor / CRO / Function (Zone) / Milestone / Defect Type / Rework Time / User/Operator / Time Period

**Unit of Measure**

Percentage

**Business Driver / Benefit Statement**

Understand the extent to which documents have to be re-worked.

**Additional Analysis on a "for cause" basis**

**Reporting Frequency**

**Threshold Target**

Defined by organization

**Companion Metrics**

Quality metrics, as driving higher completeness could compromise quality.

**Notes (eTMF vs. Paper)**

Relevant for both paper TMFs and eTMFs.

**Notes (General)**

Assume that this is mainly for scanned documents. Do you count the impact of documents re-worked multiple times?
eTMF data enables speed and ease with metrics

Issues in paper TMF metrics
- Some metrics do not apply (scanning quality)
- Many may be labor-intensive

For paper TMF, consider a risk-based approach to make metrics practical and cost-effective
- Focus on a subset: high risk content, critical trial process, critical path trial, new personnel, signals from audits
FURTHER ANALYSIS ON METRICS
Insight requires relevant information that reveals actionable details about a process.

For metrics to be meaningful and actionable, they often must be broken down to a more granular level.

The Working Group has provided a list of 17 types of analysis that may be useful in understanding trends and identifying issues.
For sponsor, determine performance of trials for a specific CROs or compare performance across CROs

Purpose: Analyze performance of partners, compare against Service Level Agreements, compare against each other

Examples:
- TMF Completeness or number of misfiled documents for all studies run by a specific CRO
- Comparison of time to process documents for all of a sponsor's CROs
• Determine overall performance for documents related to a specific country or compare performance across countries (including site level documents)
  – **Quality**: to determine how units in the country are performing
    • Example: level of completeness in a specific country may reflect on responsible managers in that country
  – **Study Knowledge**: Improve knowledge of and forecasting for specific countries
    • Example: Average number of regulatory documents per country

Produced by TMF Reference Model
- Determine performance for one selected time period or by comparing multiple time periods
- Purpose: Analyze improvements, compute return on investment (e.g. adding more staff or increasing training).
- Example:
  - Average TMF Timeliness (Processing) time for each of the last 12 months
  - Average TMF Timeliness (Processing) time for Q1 of this year vs. Q1 of last year
The following reports are some examples that provide useful information about TMF health, content and processes. These are just examples – not meant to imply that these are required or complete.

General Good Practices:
- Provide an actionable level of detail
- Properly label reports and ensure that what they represent is clear
- Choose a report format that offers the most insight (bar, pie, scatter, etc.)
- As always, if you are using an eTMF, review what your system can offer you
This report represents a snapshot of the completeness of a single study at the current time decomposed by Country. It shows the number of final, overdue, coming due and not yet due documents for each country.

The same report could be generated by Organization, Business Unit, Category/Zone, Therapeutic Area, or Program.
This chart represents a snapshot of the completeness of a single study at the current time.
This chart represents average completeness for each milestone across a collection of studies at a given time, e.g., all oncology studies.
This chart represents a collection of studies and quality defects found during a selected time period, e.g., Q4 2013.
This chart represents the breakdown of documents by type for all studies.
Design of a Metrics Program

- **Goal Selection**
  - Quality by design
- **Choosing metrics to support your goals**
  - Cost – benefit analysis
  - Support for risk-based approaches
Quality by Design and TMF Metrics

**Quality by Design (QbD):** designing and developing processes to ensure that a **product** (TMF in this case) consistently attains a **predefined quality** at the end of the process.

When applied to eTMF, QbD involves identifying **key parameters** that affect quality and risk, and monitoring those parameters … achievable only when a metrics program is in place.
• Goals supported by metrics may come out of QbD sessions, audit findings, or many other sources. Examples:
  – Audit readiness
  – Decreased processing time
  – Improved capacity planning
• Make sure metrics goals support and align with overall organizational goals
• Choose an achievable set of goals and determine which specific metrics best support them
• Consider a phased approach, i.e. introducing metrics gradually
  – Low hanging fruit could be targeted first
  – Once baseline metrics are available and understood, introduce escalation and personal responsibility, objectives and penalties
An example of applying QbD to eTMF is documented in “The New Gold Standard: Pfizer's Quality by Design Approach to Trial Management”, Pharmaceutical Executive, April 2013

- Business Case
- Solution Overview
- Critical-To-Quality attributes
### Cost vs. Benefit

- **How important is the business driver?**

<table>
<thead>
<tr>
<th>Metric #</th>
<th>Metric Type</th>
<th>Metric Title</th>
<th>Category</th>
<th>Metric Indicator</th>
<th>Part of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Completeness</td>
<td>TMF % Complete by Due Date</td>
<td></td>
<td>Lagging</td>
<td>Conduct</td>
</tr>
</tbody>
</table>

**Definition**

Percent of documents whose due date has passed that have undergone all necessary review, approval or QC processes and are considered final.

**Formula / Example**

Count of documents due by today's date that have been finalized / count of documents that were expected by today's date and finalized

**Unit of Measure**

Percentage

**Business Driver / Benefit Statement**

Ensure that the TMF is complete for purposes of decision-making and audit readiness at all times.

**Additional Analysis on a “for cause”**

Reporting Frequency

Monthly or in advance of milestones

Threshold Target

Defined by organization

Produced by TMF Reference Model
Ensuring quality is daunting… but what if you were managing a trial conducted in dozens of countries and over a thousand sites…

Defining a risk based approach is essential for success.
Applying a Risk Based Approach

• Identify which processes are more high risk. Examples:
  – 100% QC checks might be required for IP Greenlight documents, a lesser percentage for other processes or milestones
  – Countries with more complex regulatory processes
  – Sites with a high number of screening failures or protocol deviations
  – Document types commonly examined by inspectors
  – Content that affects patient safety

• Take into account reliability of document source
  – E.g. validated pharmacovigilance system vs. desktop scanning

• Establish and monitor confidence levels
METRICS PROGRAM
IMPLEMENTATION
1. Logistics (data population)
2. Accountability
3. Frequency
4. Presentation
5. Triggered activity & escalation
1. Logistics

- For each metric; define how it will be populated and how it will be shared
- Consider the benefit of ‘self service reports’ vs circulation via email at scheduled frequencies
- For eTMFs, evaluate the use of pre-existing BI tools to supplement the eTMF toolset
- Remember to consider security and appropriateness of report vs audience
2. Accountability

- Remember the TMF includes documents from a multitude of functions; so a central, cross functional ‘Business Owner’ is advisable
- Consider generating a RACI (Responsible, Accountable, Consulted, Informed) to clarify who will be generating the metrics vs. who is accountable for their contents
### Example of eTMF RACI

<table>
<thead>
<tr>
<th>Activity (short description of interface /relevant task)</th>
<th>Sponsor</th>
<th>CRO</th>
<th>eTMF provider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Create &amp; circulate SLA Report</td>
<td>I</td>
<td>I</td>
<td>R</td>
</tr>
<tr>
<td>Monitor Service Level Agreements (SLA) – Sponsor</td>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitor SLA – CRO</td>
<td>I</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Monitor SLA - eTMF provider</td>
<td>I</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>SLA Oversight</td>
<td>A</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Create &amp; circulate Close-out Timeline Report</td>
<td>I</td>
<td>I</td>
<td>R</td>
</tr>
<tr>
<td>Monitoring Close-Out Timeline /Milestones</td>
<td>A</td>
<td>R</td>
<td>I</td>
</tr>
</tbody>
</table>

Produced by TMF Reference Model
3. Frequency

- Link frequency to the Business Benefit or Benefit Statement. What period of data and associated frequency is required?
- Do all users need the report at the same frequency and same view of data?
  - Study Managers might need a monthly report
  - CRO Account Manager may only need quarterly summary.
4. Presentation

- Most people find graphics easiest to interpret
- Consider different views for different time periods, e.g.
  • 6 month view cumulative graph of submissions
  • Summary table of monthly detail
- Systems that allow drill through or data expansion offer most flexibility
- Use colour & formatting (e.g. traffic lights) to enhance tabular reports
- If using a portal consider:
  • frequency of data archival
  • benefit of keeping comparator data available e.g. 2013 data vs 2014
5. Triggered activity & escalation
   – You’ve distributed the metrics report – what next?
   – How can you promote and measure compliance to reacting to the data?
     • Define Workflow
     • Define responsibilities in RACI
     • Personal objective tie-in
     • Management accountability
     • ‘Metrics on metrics’
Business Processes – Role of Partners

• Depending on Metrics introduced partners can be metrics providers or report receivers or both
• Metrics can be linked to contracts and SLA and it’s advisable to create template reports and specific CRO generation/review responsibilities within contracts
• Comparison between different CROs and CRO vs Sponsor users can aid future decision making and promote healthy competition
• Define timelines for review at point of introduction
• Ensure the Business Drivers and/or Benefit Statements are valid and being met
• Some metrics may become redundant as your eTMF model matures; circulating superfluous information is pointless
• ‘Quality’ is key – do not lose sight of this
FINAL THOUGHTS AND SUMMARY
Available Materials

- This presentation
- Metrics Definition spreadsheet covering metrics definitions, analyses, roles and glossary
“If a measurement matters at all, it is because it must have some conceivable effect on decisions and behaviour. If we can't identify a decision that could be affected by a proposed measurement and how it could change those decisions, then the measurement simply has no value”

— Douglas W. Hubbard, How to Measure Anything: Finding the Value of "Intangibles" in Business
Opposing Forces in TMF Quality

- Law of Unintended Consequences: actions always have effects that are unanticipated or unintended.
- Need to ensure that any effort to improve one of the key metrics doesn’t result in degradation in other areas.
Conclusions

• Metrics are needed to provide the insight to manage risk and to implement true process improvements
• Up-front investment in a well-designed metrics program can improve efficiency and increase compliance
• Implement a program that
  – Drives the behavior that you want
  – Provides the information needed to make good decisions
• Involve the business across your organization – don’t start with technology but understand what technology can do for you
Thank you

Chair of TMF Reference Model Metrics and Reporting Subteam:
– Kathie Clark, kclark@wingspan.com

Join the LinkedIn group TMF Metrics

The full set of materials can be found on the TMF Reference Model site: http://tmfrefmodel.com/resources-2/